EDITORIAL (SEE HALLER ET AL., P. 2041)

Umbilical Cord Blood and Type 1 Diabetes

A road ahead or dead end?

It is our anticipation and hope that stem cells will cure type 1 diabetes someday because of their limitless capacity to differentiate as needed into the vital tissue or organ.

In theory, pluripotent cells have the capacity to reprogram a hostile immune response to tolerate pancreatic β-cells and to regenerate pancreatic β-cell mass. These two factors are the necessary ingredients for reversing type 1 diabetes. However, in practice there are many unanswered scientific questions that need clarification before we claim success.

In this issue of *Diabetes Care*, Haller et al. (1) report their interim results about autologous umbilical cord blood infusion into young children with type 1 diabetes. Children aged >1 year who developed type 1 diabetes and had banked umbilical cord blood at an approved center were recruited into this study at the University of Florida. Cord blood infusion was performed after the diagnosis of type 1 diabetes at a mean time of 4.1 months (range 2.5–7.1) and into children with a mean age of 5.5 years (3.1–7.3). The children were brought back for clinical, metabolic, and immunologic evaluation at 3, 6, 9, and 12 months after umbilical cord blood transfusion. Ethics considerations prevented infusion of umbilical cord blood into an age-matched nondiabetic control group, so an age-matched group of type 1 diabetic subjects was used for comparison. This constraint, although suboptimal, will be necessary in future stem cell type 1 diabetes trials but should not significantly compromise our ability to interpret the study outcomes.

The results of the present study are uniformly negative; umbilical cord blood infusion failed to improve C-peptide, insulin utilization, and A1C and did not increase regulatory T-cell (Treg) levels at 12 months. Assuming that the 24-month results will also fail to demonstrate efficacy in curing or ameliorating type 1 diabetes, how do we navigate the clinical complexities of stem cell trials for type 1 diabetes? Not only are there several potential cell sources that might be used for type 1 diabetes (e.g., mesenchymal stem cells, hematopoetic stem cells, adipose-derived stem cells, and umbilical cord blood), but we must also identify the appropriate conditions for expanding these cells, selecting the appropriate subpopulations of cells, and administering the proper cell dose.

The rationale for testing umbilical cord blood in young children with type 1 diabetes is primarily related to safety. Indeed, the results to date suggest that umbilical cord blood infusion is without side effects and can be given safely to children with type 1 diabetes. The matter of efficacy is more problematic. The present study gives us a strong negative signal that simple umbilical cord blood infusion might not provide a road forward toward curing type 1 diabetes. Two important considerations need to be resolved before we can reach this final conclusion: *1*) the dose of umbilical cord blood in this study might be suboptimal to reverse type 1 diabetes and *2*) a transient rise in Tregs bearing $CD4^+CD25^+$ surface markers was observed at 6 months after umbilical cord blood but not at 12 months. These two issues are interrelated because a suboptimal dose of umbilical cord blood might provide neither the critical mass of Tregs to control autoimmunity nor the requisite number of stem cells to increase pancreatic β-cell mass. Improvements in cryopreservation techniques and expansion of umbilical cord blood stem cells prior to therapeutic infusion might overcome these problems in the future.

Although at present we have no roadmap for the use of stem cells to reverse type 1 diabetes in children, two promising research discoveries might provide us with clues for future clinical trials. Recently, Zhao et al. (2,3) used human umbilical cord blood stem cells to reverse type 1 diabetes in nonobese diabetic (NOD) mice. These investigators developed coculture techniques by mixing nondiabetic human umbilical cord blood stem cells with NOD mouse spleen cells to generate an unconventional subset of Tregs bearing $CD4^+CD62L^+$ but not $CD25^+$ on the cell surface. These unconventional Tregs, when injected into diabetic NOD mice, reversed type 1 diabetes 75% of the time and stimulated pancreatic β-cell regeneration. Conventional Tregs bearing $CD4^+CD25^+FoxP3^+$ (note FoxP3 is a transcription factor that demarcates functional Tregs) did not possess these regenerative properties. These unconventional $CD4^+CD62L^+$ cells could only be derived using purified human cord blood stem cells from healthy donors but not from type 1 diabetes donors (Y. Zhao, personal communication). Apparently, healthy umbilical cord blood possesses a critical stem cell population capable of reeducating and transforming diabetic regulatory cells into regenerative $CD4^+CD62L^+$ cells capable of reversing type 1 diabetes. Conversely, umbilical cord blood obtained from individuals who later developed type 1 diabetes does not contain this critical stem cell population and therefore might not be a useful source of regenerative cells. Although there is danger in extrapolating insights gained from studies in NOD mice to children with type 1 diabetes, this nevertheless might explain why the present study has failed so far. Maybe conventional Tregs bearing $CD4^+CD25^+$ on their cell surface are the wrong regenerative cell population? In addition, Bluestone and colleagues (4) demonstrated that conventional polyclonal $CD4^+CD25^+$ Tregs were minimally effective at reversing type 1 diabetes in NOD mice, but purified antigen-specific $CD4^+CD25^+$ T-cells reversed type 1 diabetes in 60% of NOD mice. Here also, if we permit extrapolation from mouse to human, we encounter a potential problem with umbilical cord blood infusion in type 1 diabetic children because umbilical cord blood cells contain primarily polyclonal Tregs. Future stem cell trials for children with type 1 diabetes will inevitably lean on discoveries made in rodent models of the disease, inherent limitations notwithstanding. It behooves us to use our translational science wisely to sort out the limitless variables that are likely to complicate human stem cell trials for type 1 diabetes.

In summary, the present study using umbilical cord blood infusion in children with newly diagnosed type 1 diabetes has

provided us with important information about the safety of such a therapy. Unfortunately, it does not move us very far forward in discovering an efficacious therapy to reverse type 1 diabetes. By integrating new information from the laboratory into clinical trial design, we can hopefully shortcut the road to curing type 1 diabetes with stem cells. Otherwise, we may travel down many dead ends before we find a road ahead.

DAVID BLEICH, MD

From the Division of Endocrinology, Diabetes, and Metabolism, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey.

Corresponding author: David Bleich, bleichda@umdnj.edu.

DOI: 10.2337/dc09-1456

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

References

1. Haller MJ, Wasserfall CH, McGrail KM, Cintron M, Brusko TM, Wingard JR, Kelly SS, Shuster JJ, Atkinson MA, Schatz DA. Autologous umbilical cord blood transfusion in very young children with type 1 diabetes. Diabetes Care 2009;32:2041–2046
2. Zhao Y, Lin B, Darflinger R, Zhang Y, Holterman MJ, Skidgel RA. Human cord blood stem cell-modulated regulatory T lymphocytes reverse the autoimmune-caused type 1 diabetes in nonobese diabetic (NOD) mice. PLoS One 2009;4:e4226
3. Zhao Y, Wang H, Mazzone T. Identification of stem cells from human umbilical cord blood with embryonic and hematopoietic characteristics. Exp Cell Res 2006;312: 2454–2464
4. Tang Q, Henriksen KJ, Bi M, Finger EB, Szot G, Ye J, Masteller EL, McDevitt H, Bonyhadi M, Bluestone JA. In vitro-expanded antigen-specific regulatory T cells suppress autoimmune diabetes. J Exp Med 2004;199:1455–1465